Remarks

Claims 1-28 were pending in the subject application. By this Amendment, claims 1-9, 13-14, 17, 19-22, and 24-28 have been amended, claims 11 and 23 have been canceled, and new claims 29-46 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-10, 12-22, and 24-46 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The Office Action indicates that the Declaration of record is defective because it contains non-initialed alterations. Pursuant to 37 C.F.R. §§ 1.63 and 1.67, submitted herewith is a supplemental Declaration and Power of Attorney meeting the requirements of 37 C.F.R. § 1.52(c).

The drawings of record are objected to for the reasons indicated by the draftsperson on form PTO-948. Submitted herewith are formal drawings meeting the requirements of 37 C.F.R. § 1.81-1.85 to replace the drawings of record in the subject application.

The applicants gratefully acknowledge the Examiner's careful review of the subject specification. The applicants respectfully request that the specification of record be replaced with the substitute specification submitted herewith. The subject specification has been reviewed for typographical errors. No new matter is added.

The applicants respectfully request clarification regarding the status of claims 18, 19, and 22. The Office Action Summary indicates that claims 18, 19, and 22 are rejected; however, the Detailed Action does not set forth a rejection of these claims. In view of the lack of agreement between the Office Action Summary and the Detailed Action, the applicants respectfully request clarification as to the status of claims 18, 19, and 22, so that they may have an adequate opportunity to respond, if necessary.

Claims 1-17 and 24-28 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description and as non-enabled by the subject specification. The applicants respectfully submit that the claimed invention is sufficiently described and enabled by the subject specification. However, by this Amendment, the applicants have amended claims 1 and 25 to recite that the protease inhibitor interacts with amyloid beta-peptides within the brain tissue of the

transgenic mouse. Support for this amendment can be found, for example, at page 15, lines 1-7, page 16, lines 24-27, page 38, lines 5-11, and Figure 8 of the specification as originally filed. Thus, the claims require that the expression product of the protease inhibitor gene has the recited biological function, *i.e.*, interaction with amyloid beta-peptides within the brain of the transgenic mouse. At page 12, the Office Action comments on the significance placed on ACT's amyloid beta-peptide interaction domain within the Nilsson *et al.* publication (*J. Neurosci.* 21:1444-1451, 2001). Thus, the recited protease inhibitors also have the ability to interact with amyloid beta-peptides and an Alzheimer's-like phenotype would be expected. The applicants have also amended claim 2 to recite that expression of the protease inhibitor gene increases the rate or extent of amyloid formation in the brain tissue of the transgenic mouse. Support for this amendment can be found, for example, at page 15, lines 8-16 and lines 25-32, and page 17, lines 22-32, of the specification as originally filed.

At page 6, the Office Action indicates that the phenotype of a transgenic mouse comprising a transgene encoding a protease inhibitor that is not expressed in neuronal cells will have little or nothing in common with the mice of the claimed invention. However, as indicated at pages 16-17 and 25-26 of the specification as originally filed, the promoter used for the ACT experiments in the examples was a modified glial fibrillary acidic protein (GFAP) promoter. The modified GFAP promoter was selected because it is astrocyte-specific, and the antichymotrypsin gene is overexpressed in astrocytes in human Alzheimer's disease sufferers, as indicated at page 16, lines 19-27, of the specification. Furthermore, in view of the demonstrated effectiveness of the modified GFAP promoter and the guidance provided at page 16, lines 1-6, of the specification as originally filed, those of ordinary skill in the art would appreciate that promoters for expression of the protease inhibitor gene in other cells of brain tissue, such as neurons, could also be utilized. Examples of brain-specific promoters that can be used include, but are not limited to, the platelet derived growth factor (PDGF) promoter, the Thy-1 promoter, the prion gene promoter, and the neurofilament light or heavy chain promoter.

In regard to the comments at page 8 of the Office Action, the applicants respectfully submit that the compounds recited in claim 28 are art-recognized and well known to those of ordinary skill in the art. For example, inhibitors of the interaction between the amyloid beta-peptide and antichymotrypsin include peptides composed of all or part of amino acids 1 through 15 of the A beta-

peptide, peptidomimetics related to this sequence of amino acids, or small molecules designed to mimic the sequence. It is known that antichymotrypsin binds to the N-terminus of the beta-peptide because that sequence contains Asp-Ser-Gly sequence, which is characteristic of the active site of serine proteases, and is the normal target of the antichymotrypsin anti-protease. Thus antichymotrypsin binds to a beta because A-beta resembles a protease. Any compound that interferes with the active inhibitory site of antichymotrypsin, such as a protease-related peptide, or small molecule that effectively mimics that peptide, will prevent antichymotrypsin from binding to beta-peptide and it would be testable in the transgenic mouse models of the subject invention. Similarly apolipoprotein E binds to the A beta-peptide between amino acids 12 and 28. Peptides corresponded to the sequence prevent the interaction between apolipoprotein E and the beta-peptide and can be used to inhibit amyloid formation or to test for the possibility of it hitting amyloid formation in the transgenic mice. Submitted herewith for the Examiner's consideration are U.S. Patent Nos. 6,214,569; 5,780,587; and 5,338,663, which describe inhibitors of the interaction between the amyloid beta-peptide and antichymotrypsin and their identification. Accordingly, reconsideration and withdrawal of the written description and enablement rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 7, 24, 25-28 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that the claims are not indefinite; however, by this Amendment, the applicants have amended claims 7 and 24 to lend greater clarity to the claimed subject matter. The applicants have replaced the term "derived" with the term "established" in claim 7, and have replaced the term "transgenic animal" with the term "transgenic mouse" in claim 24, as recommended by the Examiner. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 1-3, 5, 6, and 8 are rejected under 35 U.S.C. §102(a) as being anticipated by Mucke *et al.* (*Soc. Neurosci. Abstr.*, 1999, 25:302). The applicants respectfully submit that the Mucke *et al.* abstract is not prior art to the claimed invention. Submitted herewith for the Examiner's consideration is a Declarations under 37 C.F.R. § 1.131 by Drs. Nilsson, Potter, and Arendash, the inventors of the claimed invention, with two accompanying Exhibits. As indicated in their Declarations, prior to October 24, 1999, the inventors produced a transgenic mouse having a genome

containing a first transgene encoding human antichymotrypsin (hACT) and a second transgene encoding human amyloid precursor protein (hAPP), wherein the first transgene was operably linked to a modified glial fibrillary protein (GFAP) promoter capable of driving expression of the hACT transgene within the transgenic mouse at sufficient levels to cause an increase in amyloidosis, as evidenced by Exhibits A and B, which accompany the Declarations. As indicated in their Declarations, founder mice carrying the ACT transgene were utilized to produce the double transgenic (hACT/hAPP) mice (see, for example, pages 1-3 of Exhibit B and pages 25-28 and 34-38 of the specification). Expression of the two transgenes was detected in the brain tissue of the mice, and amyloid-β (Aβ) peptide complexed with hACT was detected. Thus, the applicants respectfully submit that the claimed invention was conceived and reduced to practice prior to the publication date of the Mucke *et al.* abstract. Therefore, the Mucke *et al.* abstract is not prior art against the claimed invention. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a).

Claims 1, 5, 6, and 8 are rejected under 35 U.S.C. §102(b) as being anticipated by either Yeung *et al.* (*J. Cell. Biochem. Suppl.*, 1994, 0:164) or Kuljis *et al.* (*Soc. Neurosci. Abstr.*, 1993, 19:1035). The applicants respectfully submit that the Yeung *et al.* and Kuljis *et al.* publications do not provide an enabling disclosure of the claimed invention. Both the Yeung *et al.* and Kuljis *et al.* publications are abstracts that report transgenic mice carrying a human α1-antichymotrypsin transgene. However, the abstracts do not provide any information concerning the genetic constructs used to produce the transgenic animals beyond identification of antichymotrypsin as the transgene. For example, neither publications describe the promoters utilized to achieve expression of the antichymotrypsin transgene with the mouse brain, or whether the transgene was expressed in neurons or glia. As the Examiner is aware, in order to anticipate, a single reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). The applicants respectfully assert that the cited reference does not teach or suggest each and every element of the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) is respectfully requested.

Claims 1, 7, 10, 12, 13, and 15-17 are rejected under 35 U.S.C. §103(a) as being obvious over Mucke *et al.*, Yeung *et al.*, or Kuljis *et al.* in view of Snow *et al.* As indicated above in response to the rejections under 35 U.S.C. §§ 102(a) and 102(b), the Mucke *et al.* abstract is not prior art to the claimed invention, and the Yeung *et al.* and Kuljis *et al.* abstracts do not provide an enabling disclosure of the claimed invention. The Snow *et al.* publication describes a transgenic animal carrying a transgene encoding perlecan, but does not teach or suggest the transgenic animals of the claimed invention. Therefore, the Snow *et al.* publication does not cure the deficiencies of the primary references (Mucke *et al.*, Yeung *et al.*, or Kuljis *et al.*). In view of the foregoing remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

Claims 20 and 21 are rejected under 35 U.S.C. §102(b) as being anticipated by Kobayashi *et al.* (*Neurosci. Lett.*, 1994, 172:147-150). The applicants respectfully submit that the Kobayashi *et al.* publication does not teach or suggest the claimed methods. However, by this Amendment, the applicants have amended claims 20 and 21 to lend greater clarity to the claimed subject matter. By this Amendment, the applicants have amended claim 20 to recite the additional step of determining whether the compound promotes or inhibits the activity of the protease inhibitor to promote or inhibit cell death or cell division, and have amended claim 21 to recite the additional step of determining whether the compound promotes or inhibits the activity of the protease inhibitor to promote or inhibit neurite outgrowth. As indicated in Figure 3 and its caption at page 149 of the Kobayashi *et al.* publication, cultures were treated with $\beta_{25\text{-}40}$ in the absence or presence of antichymotrypsin (ACT). However, in order to determine whether the compound ($\beta_{25\text{-}40}$) promotes or inhibits the activity of ACT to promote or inhibit cell death or cell division, or neurite outgrowth, the opposite method would have to be carried out, *i.e.*, the cultures would have to be treated with ACT in the presence or absence of $\beta_{25\text{-}40}$. Therefore, the Kobayashi *et al.* publication does not teach or suggest the applicants' claimed methods. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) is respectfully requested.

Claims 24-26 are rejected under 35 U.S.C. §102(b) as being anticipated by Snow *et al.* (WO 97/46664) as evidenced by Anger *et al.* (*Neurotoxicol*, 1991, 12:403-413). The applicants respectfully submit that the Snow *et al.* publication does not teach or suggest the use of a radial arm water maze having an escape platform capable of relocation among the radial arms of the maze, as

recited in claim 24, and described at pages 32 and 33 of the subject specification as originally filed. The Anger *et al.* publication merely cites other publications as indicating that the Morris Water Maze and radial arm maze, which are two separate tests, can be used to evaluate learning and memory. Neither the Snow *et al.* or Anger *et al.* publications teach or suggest the claimed method utilizing a radial arm water maze. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Please also note the addition of new claims 29-46, which recite a transgenic mouse whose genome comprises at least one transgene comprising a nucleic acid sequence encoding a protease inhibitor operably linked to a promoter, and some of which recite a second transgene comprising a nucleic acid sequence operably linked to a promoter. Support for these claims can be found, for example, at page 8, lines 17-33, page 9, lines 1-10, and pages 12-14 of the specification, as well as the claims as originally filed.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachments: Petition and Fee for Extension of Time
Supplemental Declaration and Power of Attorney
Formal Drawings
Substitute Specification
Statement under 37 C.F.R. §1.125(b)
Declarations under 37 C.F.R. § 1.131 by Drs. Nilsson, Potter, and Arendash, with Exhibits A and B
U.S. Patent Nos. 6,214,569; 5,780,587; and 5,338,663